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U.S. - China Joint Commission on Commerce and Trade
Pharmaceuticals and Medical Devices Subgroup
Pharmaceutical Task Force Meeting Summary
April 8 - 9, 2008
Guilin, China

Overview

The Pharmaceutical Task Force of the U.S. – China Joint Commission on Commerce and Trade (JCCT) Pharmaceutical and Medical Device Subgroup met in Guilin, China on April 8 - 9, 2008.

The U.S. Delegation to the April 2008 Pharmaceutical Task Force meeting was led by Mr. Jeffrey Gren, Director of the Office of Health and Consumer Goods (OHCG) at the U.S. Department of Commerce (DOC) and consisted of DOC and USTR officials and representatives from major U.S. pharmaceutical trade organizations. Those pharmaceutical trade organizations were Pharmaceutical Research and Manufacturers of America (PhRMA), Generics Pharmaceutical Association (GPhA), International Pharmaceutical Excepients Council (IPEC), and the Research & Development Pharmaceutical Association of China (RDPAC).

The Chinese Delegation consisted of China's State Food and Drug Administration (SFDA) officials and a representative from the China Pharmaceutical Industry Association.

See Attachment A for a list of the U.S. and Chinese delegations.

Meeting Agenda:

I. OPENING PLENARY SESSION
II. CHINA DRR (DRUG REGISTRATION REGULATION) AND DAL (DRUG ADMINISTRTION LAW)
III. PARTNERSHIP WITH SFDA ON CHINA'S DRUG REGULATION SYSTEM
IV. SFDA CENTER OF DRUG EVALUTAION'S GUIDANCES
V. REVIEW OF 2008 WORK PLAN
VI. CONTROL OF RAW MATERIALS AND UTILIZATION OF DMF
VII. CLOSING
VIII. WORKSHOP ON RAW MATERIAL CONTROL:
    a. DMF/CEP(COS) for API
    b. Supply Chain Security and Excipient Qualification

I. OPENING PLENARY SESSION

Chang Wenzuo, China Subgroup Co-chair and Counsel, SFDA Dept. of International Cooperation: Chang Wenzuo welcomed the US DOC delegation and thanked Mr. Gren and the US Department of Commerce for continued effort during the past eleven years in improving the trade relations between the US and China and the quality of pharmaceuticals and medical devices

in China. He also thanked the local Guilin SFDA Office for providing such a beautiful location and arranging the logistics for the meeting. Chang Wenzuo then introduced the China delegation and he wished the success of this 12 year anniversary JCCT Pharmaceutical and Medical Devices Subgroup meeting.

Jeffrey Gren, Director, Office of Health and Consumer Goods, USDOC: Mr. Gren thanked SFDA for hosting the meeting in Guilin, and he introduced the U.S. delegation members. Mr. Gren stressed the importance of the JCCT Subgroup meeting and briefly outlined the achievements the JCCT Subgroup has made during the past eleven years. Mr. Gren explained that USFDA did not participate in the delegation due to scheduling conflicts related to the MOA with SFDA, and pointed out that based upon discussions with USFDA, he expects USFDA to participate in future Subgroup meetings. Mr. Gren added that once USFDA opens an office in Beijing, it will be easier for USFDA staff to participate in future Subgroup meetings in China. Mr. Gren pointed out that DOC believes that it is important to have industry participate in this governmental to government JCCT Subgroup, and that he is pleased to see Chinese industry's participation in this meeting. Mr. Gren closed his remarks with an outline of the JCCT Subgroup activities for the rest of the week.

At this point the opening plenary concluded and the delegation split into separate rooms for the concurrent Pharmaceuticals and Medical Devices Task Force Meetings. Following is a summary of the Pharmaceutical Task Force meeting. A summary of the Medical Devices Task Force meeting is included in a separate document.

II. CHINA DRR (DRUG REGISTRATION REGULATION) AND DAL (DRUG ADMINISTRTION LAW)

Pharmaceutical Task Force US Co-chair Jeffrey Gren: Mr. Gren briefly reviewed the progress and status of the U.S. comments on China's Drug Regulatory system, and invited SFDA to present the update. He also invited the U.S. industrial representative to ask further questions following SFDA's presentation.

Pharmaceutical Task Force China Co-chair Mr. Wei Zhang, Director General, SFDA Department of Drug Registration: DG Zhang stated that the purpose of the meeting is "information exchange and open communication." Under the partnership, SFDA's goal is to increase training opportunities. For example, after this meeting, local SFDA officers will join the quality of pharmaceutical raw materials and the vaccine roundtable training programs. Also, SFDA has invited vaccine manufactures (Chinese and international companies) to participate in the vaccine roundtable training. He then invited US representatives to ask specific questions on China's DRR.

Mr. Harrison Cook (Representing PhRMA): Mr. Cook asked the following questions:

- Concerning the clinical trial application (CTA) processes, specifically the revised/enhanced clinical trial protocol, the U.S. does not require new CTA for subsequent trials for review. The EU does require new CTA and the review takes

only 30-60 days. What's the timeline for SFDA? Would SFDA consider an expedited review for new protocols?

- What is the status of the new Drug Registration Regulation and what is the anticipated implementation date?

- What would be the changes in SFDA after folding into MOH (Ministry of Health)?

DG Zhang Wei: Answer to the first question is that SFDA is considering more a flexible and timely review on additional data for CTA. Answer to the second question is that the new DRR demonstrated SFDA's effort in making the application and review process open and transparent. SFDA requested comments on line twice, and discussed with industries as well. SFDA also considers international practices by FDA, EU, etc. SFDA considered the balance between innovation and generic. The new DRR was implemented on October 1, 2007, and since its implementation has received favorable and positive feedback. However, there are some concerns on the review and approval process. Due to technical issues, SFDA may publish supplementary revisions this summer. SFDA has never slowed down the review for innovative drug and multi-center clinical trial data. JCCT is very helpful for SFDA to do a better job and to improve. Practically speaking, it is quite difficult for SFDA to significantly speed up the review time currently, due to limited resources. Comparing the work load between SFDA and USFDA, SFDA has much heavier work load. SFDA wants to ensure the quality. We believe that improving SFDA staff's quality is a key for us to make real improvements. SFDA has drafted a plan for training with FDA and EMEA. With the globalization, many innovative drugs are coming into Chinese market. Our question is - "are we ready?"

In response to how SFDA would change after folding into MOH (Ministry of Health), changes have been identified by the State Council. The drug side will not change much. For food registration and regulation, there will be a switch over of responsibilities; regulation of food will be done by SFDA. Internal departments may be streamlined and responsibilities further clarified. The bottom line is to do better in the regulation of drug and food, and to reduce redundancy. One direct change is that the SFDA Commissioner and the Deputy Minister of MOH will report to the Minister of MOH, rather than the State Council.

Harrison Cook (Representing PhRMA): Mr. Cook asked about Article 18 to China's Drug Registration Regulation (DRR) and his understanding that statements of non-infringement of patents by generic applicants would be published and that disputes could be resolved through normal patent dispute processes. PhRMA welcomed this but wondered where the information would be published and, in the case of a dispute, if SFDA would stay their review. Mr. Cook also indicated that, with respect to data protection, there was still much misunderstanding regarding China's policies and they hoped that SFDA would provide a point of contact to establish a more thorough discussion with industry on this issue to ensure implementation of Article 20. PhRMA reiterated its request that the definition of "new chemical entity" (NCE) be clarified in China's laws and regulations.

DG Zhang Wei: He commented that data exclusivity and patent linkage have been difficult topics in past JCCT meetings and are not on today's agenda. Zhang Wei said he would like to provide an update on these topics. He indicated that under Article 18 SFDA will protect patents

by posting patent related information from applications, including generic applicants' assertions of non-infringement on an accessible web-site. This would also provide a platform for questions by industry to be submitted to SFDA. Industry may also submit information regarding patent infringement, which is a big change in the Drug Registration Regulations (DRR) and was included based on recommendations from PhRMA. It appeared that it would be the responsibility of industry to regularly check the website. Zhang Wei also indicated that this platform would provide patent information to generic applicants.

With respect to data protection, Zhang Wei noted that this was an old topic for the Subgroup, and that is a complicated issue and intertwined with other issues. Zhang Wei noted that data protection had been the source of many disagreements between developed and developing countries. That said, he assured the Subgroup that SFDA wanted to take a "proactive" role in addressing this issue and will be doing further research. Zhang Wei noted that he asked Mac Lumpkin Deputy Commissioner of USFDA a question about harmonization during an international conference, and Dr. Lumpkin responded that harmonization does not necessarily mean all countries have the same requirement, but rather it means coordination and cooperation.

Harrison Cook agreed with Dr. Lumpkin's statement, and Jeffrey Gren, the U.S. Task Force Co-chair, thanked Zhang Wei for this information.

Ms. Wu LiYa (Division Director, Dept. of Policies and Regulations, SFDA): She provided an update on the legislation plans for 2008 - clarification of prescription drug and OTC. The revision of the Drug Administration Law (DAL) will cover the time frame of 2008 to 2012. For 2008 the focus is on research, investigation and feasibility to see what should be done. SFDA is putting more information on their website, for both drugs and medical devices. SFDA's Center for International Pharmaceutical Cooperation is improving the English version of the website.

Mr. Ding Jianhua (Division Director, Dept of Drug Registration, SFDA): He made a comment that SFDA has made improvements in the DRR.

- IND review time was reduced from 120 days to 90 days. He expects the review time to be reduced it to 80 days in the future.

- New models will be set up, not only to reduce review time, but also will set up pre-meetings, and to set up "special applications." SFDA will also clarify what is meant by "special application."

- SFDA accepts applications in CTD format. The applicant will only need to translate CTD documents into Chinese.

- Adapting to international practices, regarding IND review, there is now no need for sample testing and specification verification.

- Transparency is a big part of this revision of DRR. SFDA has made improvements on transparency and has enhanced accountability.

- You have many questions on CTA (Clinical Trial Application), particularly on review time. We are looking into review methodologies. Korea started to differentiate IND and NDA since 2002, and made the review faster. SFDA will look into that.

- To comment on Ling Ye's questions about CTD, currently both Chinese and English versions are required for an international application. The ICH format is acceptable, just translate it into Chinese. SFDA will consider eCTD in the future.

Ms. Ye Ling (Representing GPhA): Could you please give an update on the comments on DRR that GPhA submitted to SFDA on May 10, 2007?

DGZhang Wei: Regarding the requirement of local representative or office for a foreign application (Article 6), SFDA feels that this is needed, because SFDA needs to hold the applicant accountable for any potential problems. For practical reasons, a communication contact in China is needed.

Mr. Ding Jianhua: The requirement that "an application for a change in dosage form but without change in the route of administration should be made by the original license holder of the current dosage form" was deleted in the revision of the DRR that is currently in effect.

(Comment from Ling Ye, based upon reading the current version of DRR after the JCCT meeting):

- Article 88 in the older version was replaced by Article 73 in the current version, which states: "Generic drug applicant should be pharmaceutical manufacturing enterprises, where the applied drug should corresponds to the manufacturing scope described in the Drug Manufacturing Certificate.

- Article 11 and 97 in the older version was revised to the effect that during the review process "SFDA may organize an evaluation for the market value of the drug." The older version specified for a market and risk value evaluation to run parallel to the safety and efficacy evaluation. Under that framework, the market and risk value evaluation could have impacted the fate of the drug approval.

PARTNERSHIP WITH SFDA ON CHINA'S DRUG REGULATION SYSTEM

Question from the US Delegation Member: Will SFDA take an active role in the regulatory session of the East Asia Life Science and Innovation Forum which will be held in April in Japan?

Response from the SFDA: SFDA is interested in cooperation with other regulatory bodies to coordinate the efforts in the regulations of drug and medical device. Whether SFDA will participate actively in the East Asia Life Science and Innovation Forum depends on our work load and many other collaboration activities ongoing. Medical experts from China, Japan and Korea wanted to have a round table on clinical trials. Japanese experts found that Japanese and

Chinese people have genetic similarities. Japan's PDMA accepts clinical data done on Chinese populations (unilaterally). We want to go to the symposium and to learn more on these topics.

III. SFDA CENTER OF DRUG EVALUTAION'S GUIDANCES

Mr. Roy Von Kutzleben (Representing PhRMA): FDA, EMEA, ICH have guidelines on quality, clinical, pre-clinical that are accessible to industries. What are SFDA plans concerning issuing guidelines in these areas? How does SFDA plan to harmonize with international practices? What SFDA is planning to do in implementing the post-approval supplements, annual report, and CBEs? Can SFDA allow a longer time period for comments, since the guidelines need to be translated into English before foreign companies can comment. In general, what are SFDA plans for issuing guidelines?

Mr. Wei Zhang: Just as you mentioned, technical guidelines are a complicated issue. We have published more than 40 guidelines. It is complicated because when SFDA publishes new guidelines the old ones will have to be considered, changed, updated, and so on. We seek comments from industry, reference other countries' experience, and we need to consider Chinese situations.

SFDA CDE has a comprehensive plan for issuing guidelines. Currently 46 guidelines have been published by SFDA. The following factors are taken into consideration with respect to issuing guidelines:

1) Important guidelines for evaluation and having a sound international reference. For example, refer to US FDA, EMEA, and PDMA for guideline.
2) China's situation.
3) The process of issuing guidelines started in 2006. SFDA finished the draft of the third version of the guidelines. On March 28, SFDA finished the draft of six guidelines and these may be published next month. Additional guidelines will be updated and revised when new technologies and situations provide the opportunity and requirement.

Mr. Gren: Can SFDA provide us an update and summary of the discussion on SFDA - U.S. HHS MOA (Memorandum of Agreement) as it relates to pharmaceuticals and APIs?

DG Zhang Wei: Note: DG Zhang's initial response was that we should get an update on the MOA from USFDA. DG Zhang then went on discuss this issue in some detail, as outlined below:

With the US DMF system, finished dosage manufacturers are responsible for auditing the API providers, and other raw materials. As long as the audit was done, it is OK to use the DMF. For instance, with regards to the Heparin Sodium problem, some API manufactures are not registered as pharmaceutical manufacturers, and therefore are out of SFDA's jurisdiction. SFDA is willing and determined to cooperate with international regulatory bodies to address the issue. SFDA has provided a complete list of authorized suppliers of pharmaceutical products. We hope US companies will use the list to source their needed products.

SFDA will investigate and find out how many companies sell compounds that are only used for pharmaceutical products. For 10 drugs listed in the MOA, SFDA has put out announcement to ask which Chinese companies produce these products, and we will put the list out.

SFDA concerns are: 1) if the regulations for APIs are too tight, US companies may not get what they need; and 2) APIs also come from other countries into the US. In May, the new laws in China will have a lower threshold for prosecution of API providers who sell APIs to counterfeit drug manufactures.

The list of approved API providers for China can be located on the SFDA website. If the user enters the drug name in Chinese he/she will receive a list of approved providers.

SFDA is also working towards improving the environmental health. The new regulations have been published. The established manufacturers will have two years to bring the environmental safety up to the new standards. The new manufacturers will have to comply with the new regulations before getting the manufacture certificate.

SFDA also pointed out that they recently conducted an investigation of China websites that advertise APIs for medical purposes. If based upon the investigation they discover that an API is for sale through the website for a medical purpose, that has not received SFDA GMP approval, SFDA has proceeded to shut down websites that sold API for medicinal purposes without SFDA GMP approval.

IV. REVIEW OF 2008 WORK PLAN

Mr. Gren: Mr. Gren summarized the proposed pharmaceutical events on the draft of 2008 Subgroup workplan, and based upon discussion several events were modified, while a couple of events were added. Following the Task Force meeting the medical devices and pharmaceutical changes were added to the overall Workplan, which was signed by the SFDA and DOC Co-chairs during the Closing Plenary. Attachment B is a copy of the signed Workplan.

The major pharmaceutical new activities on the work plan from April 2008 to April 2009 events on the work plan include:

1) Roundtables and SFDA Delegation Visit to Europe, Japan and U.S. API & Excipient Manufacturers to focus on GMP and Supply Chain Control (Spring, Summer and Fall 2008)
2) Pharmaceuticals Quality Workshop (Quality by Design) to focus on ICH Q8/Q9/Q10 Fall/Winter 2008/2009 (China)
3) Medical Products Anti-Counterfeiting Workshop (Fall/Winter 2008/2009 - China)
4) Pharmaceutical Task Force Meeting (same week as anti-counterfeit workshop)
5) SFDA Delegation Visit to U.S. to focus on the conduct of Pharmaceutical Multi-Centered Clinical Trials
6) April 2009 Subgroup Meeting – Washington D.C.

V. CONTROL OF RAW MATERIALS AND UTILIZATION OF DMF

This session proceeded with formal Power Point presentations, followed by a discussion/question and answer period, as outlined below:

Dr. Victoria Wei (Representing PhRMA): She provided a brief presentation on what are DMF and CEP and how they can be utilized to control the quality of API. This was an abridged version of the presentation Victoria made during the Quality of Pharmaceutical Raw Materials training program during the afternoon of April 9.

Dr. David Schoneker (Representing IPEC): He made a brief presentation on raw material control, especially on excipients. This was an abridged version of the presentation David made during the Quality of Pharmaceutical Raw Materials training program during the afternoon of April 9.

VI. CLOSING PLENARY SESSION

The closing plenary began with summary comments on the accomplishments of the Task Force meetings by the Task Force Co-chairs.

Mr. Gren: Mr. Gren summarized the topics discussed and the outcome of the discussion for the Pharmaceutical Task Force. He praised the cooperation of SFDA and stated that this was the most successful JCCT Pharmaceutical Task Force meeting since he has been leading the Task Force.

DG Zhang Wei: DG Zhang added that incorporation of SFDA into MOH is aimed to enhance SFDA's effectiveness in regulating food and drug, and to reduce the redundancy of the positions and responsibilities. DG Zhangemphasized on the importance of the guidelines which SFDA is working on to further improve the regulation of drugs in China. SFDA will also enhance the English version of their website.

Mr. Richard Paddock (US DOC): Made summary comments on the activities and the agreements reached during the Medical Devices Task Force meeting. According to Mr. Paddock modest progress was made – for example, the Chinese indicated there would be no restriction in Decree 276 on ports for the import of medical devices into China, and SFDA agreed that re-registration will not be necessary for minor changes in medical devices.

Ms. Jie Gao (Division Director, Dept of Medical Devices, SFDA) – She supported Mr. Paddock's summary and added that the Medical Devices Task Force meeting included a productive exchange of information.

Following the Task Force summaries the new Subgroup Workplan for the next 12 months was signed by DOC and SFDA, and then the Subgroup Co-chairs made closing comments.

VII. WORKSHOP ON DMF/CEP(COS) AND RAW MATERIAL CONTROL

The workshop on raw materials control (DMF/CEP - COS) was conducted on April 9 in the afternoon. Dr. Victoria Wei (representing PhRMA) and Mr. Shawn Li (representing RDPAC) introduced the function and usage of DMF and CEP in applications of NDAs, ANDAs and MAAs. There were some open discussions among the participants, US industrial delegates and the panelists on DMF submission and FDA inspection practices.

The workshop on raw materials control including coverage of supply chain security and excipient qualification was conducted on April 10 in the morning. Dr. David Schoneker (representing IPEC) and Dr. Cloris Tian (representing IPEC) discussed IPEC initiatives to improve supplier qualification and control systems to be used by the pharmaceutical industry for their entire supply chain in the future. New guidelines are being developed by IPEC that may help improve communication and establish standardized processes for excipient and supplier selection and qualification.

There were more 70 people, mostly are regulatory officers from SFDA's provincial offices, participating in the workshop.

VIII. VACCINE ROUNDTABLE

Following the formal JCCT meeting, a workshop focusing on Vaccine Registration and Good Clinical Practice (GCP) was held on Friday April 4 in Guilin, China.

It is recognized worldwide that vaccines form an important part of most countries overall healthcare policy. This is due to the very significant impact vaccines have had in reducing and eradicating life threatening diseases.

In order to make the benefits of both established vaccines and the many new and innovative vaccines in development (which will offer protection against diseases associated with significant morbidity and mortality) available to everyone, it is important that national vaccine regulatory requirements do not present undue barriers to patient access. In particular regulations must protect public health and safety but they should not create unnecessary delays in making vaccines available nor should they require significant duplication of clinical research activities.

All vaccines must go through rigorous technical and clinical development programs before they are subject to detailed regulatory review. This means following internationally recognized guidelines (ie. Declaration of Helsinki) and specific national regulatory requirements such as those in the USA, EU and China. In the EU and the USA, innovator companies can obtain

formal advice and guidance from the regulatory authorities: this allows the EMEA and FDA early access to the innovators data and helps ensure that the vaccine will comply with the regulatory requirements. In order to make these vaccines available at the earliest opportunity, it is usually expedient to undertake a global development program, which includes as many countries as is feasible in the program and which facilitates parallel worldwide submissions and where possible worldwide parallel approvals.

This was the starting point of the satellite workshop, which was attended by Centre for Drug Evaluation (CDE) and SFDA staff from both central and provincial offices and local Chinese vaccine manufacturers. The head of the Vaccines Regulatory Unit within CDE, Mr. Yin, chaired the meeting, which highlighted the importance of this topic to both the CDE and the SFDA.

The main content of the presentations was on Good Clinical Practice (GCP), which is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible (as defined in ICH guideline, E6).

In practice this requires implementation of certain criteria, such as careful site selection, training and re-training and clear communication of roles and responsibilities for staff. And indeed these criteria are followed by companies conducting clinical trials in China.

Undertaking clinical development of vaccines in China, however, can be challenging because of unique aspects of the Chinese regulatory systems: the regulations make participation in global clinical trials for vaccines prohibitive; extensive testing of the biological product is mandatory and must be completed before the investigational new drug application (IND) is approved.

Overall, the workshop provided the local Chinese companies with an opportunity to better understand how multinational companies undertake GCP and also to understand how vaccine regulatory requirements are fulfilled in other regions, such as the USA and EU.

The workshop marked what is hoped to be the start of dialogue between industry and the CDE/ SFDA on vaccine registration. Indeed following the workshop, it was agreed that similar workshops and interactions, would be beneficial to all sides.